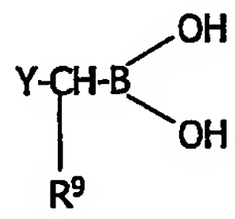
CLAIMS

1. An oral dosage form of a compound selected from boronic acids which have a neutral thrombin P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, and salts, prodrugs and prodrug salts of such acids, the dosage form comprising a solid phase formulation comprising the compound and being adapted for reconstitution of the formulation to form a liquid preparation.

2. A dosage form of claim 1 wherein the thrombin P1 domain comprises a neutral aminoboronic acid residue.

3. A dosage form of claim 1 wherein the boronic acid is of formula (I):



(I)

wherein

Y comprises a moiety which, together with the fragment $-CH(R^9)-B(OH)_2$, has affinity for the substrate binding site of thrombin; and

R^9 is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or R^9 is $-(CH_2)_m-W$ where m is from 2, 3, 4 or 5 and W is –OH or halogen (F, Cl, Br or I).

4. A dosage form of claim 3 wherein R^9 is an alkoxyalkyl group.

5. A dosage form of claim 3 wherein Y comprises

an amino group bonded to structural fragment $-CH(R^9)-B(OH)_2$, and

a hydrophobic moiety which is linked to said amino group and which, together with said structural fragment, has affinity for the substrate binding site of thrombin.

6. A dosage form of any of claims 3 to 5 wherein Y comprises an amino acid which binds to the S2 subsite of thrombin, the amino acid being N-terminally linked to a moiety which binds the S3 subsite of thrombin.

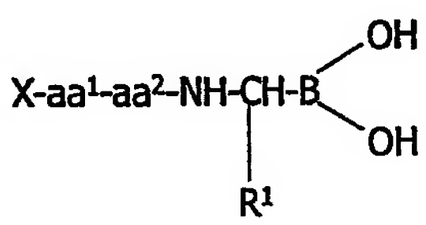
7. A dosage form of claim 6 wherein Y is an optionally N-terminally protected dipeptide which binds to the S3 and S2 binding sites of thrombin and the peptide linkages in the acid are optionally and independently N-substituted by a C_1-C_{13} hydrocarbyl optionally containing in-chain or in-ring

nitrogen, oxygen or sulfur and optionally substituted by a substituent selected from halo, hydroxy and trifluoromethyl, and optionally wherein said dipeptide is N-terminally protected and/or all the peptide linkages in the acid are unsubstituted.

8. A dosage form of claim 7 wherein the S3-binding amino acid residue is of (R)-configuration, the S2-binding residue is of (S)-configuration, and the fragment $-NHCH(R^9)-B(OH)$ is of (R)-configuration.

9. A dosage form of any of claims 1 to 8 wherein said compound is a pharmaceutically acceptable base addition salt of a said acid.

10. An oral pharmaceutical dosage form adapted to be reconstituted either
prior to administration into a liquid for oral administration, or
in the mouth,
and comprising a compound selected from boronic acids of formula (III) and salts, prodrugs and prodrug salts thereof:



(III)

where:

X is H (to form NH_2) or an amino-protecting group;

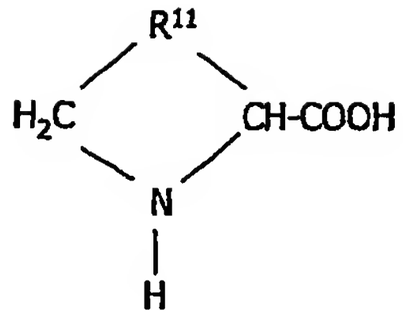
aa^1 is an amino acid having a hydrocarbyl side chain containing no more than 20 carbon atoms and comprising at least one cyclic group having up to 13 carbon atoms;

aa^2 is an imino acid having from 4 to 6 ring members;

R^1 is a group of the formula $-(CH_2)_s-Z$, where s is 2, 3 or 4 and Z is –OH, –OMe, –OEt or halogen (F, Cl, Br or I).

11. A dosage form of claim 10 wherein aa^1 is selected from Phe, Dpa and wholly or partially hydrogenated analogues thereof, and optionally is selected from Dpa, Phe, Dcha and Cha, e.g. is (R)-Phe or (R)-Dpa.

12. A dosage form of claim 10 or claim 11 wherein aa^2 is a residue of an imino acid of formula (IV)



(IV)

where R^{11} is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2=CH_2-$, $-S-CH_2-$, $-S-C(CH_3)_2-$ or $-CH_2-CH_2-CH_2-$, which group, when the ring is 5- or 6- membered, is optionally substituted at one or more $-CH_2-$ groups by from 1 to 3 C_1-C_3 alkyl groups, and optionally aa^2 is an (S)-proline residue, e.g. aa^1-aa^2 is (R)-Phe-(S)-Pro.

13. A dosage form of any of claims 10 to 12 wherein aa^1 is of (R)-configuration and/or aa^2 is of (S)-configuration and/or the fragment $-NH-CH(R^1)-B(OH)_2$ is of (R)-configuration.

14. A dosage form of any of claims 10 to 13 wherein R^1 is 2-bromoethyl, 2-chloroethyl, 2-methoxyethyl, 3-bromopropyl, 3-chloropropyl or 3-methoxypropyl, e.g. is 3-methoxypropyl.

15. A dosage form of any of claims 10 to 14 where X is $R^6-(CH_2)_p-C(O)-$, $R^6-(CH_2)_p-S(O)_2-$, $R^6-(CH_2)_p-NH-C(O)-$ or $R^6-(CH_2)_p-O-C(O)-$ wherein p is 0, 1, 2, 3, 4, 5 or 6 and R^6 is H or a 5 to 13-membered cyclic group optionally substituted by one or more (e.g. 1, 2, 3, 4 or 5) halogens (e.g. F), for example at least at the 4-position, and/or by 1, 2 or 3 substituents selected from amino, nitro, hydroxy, a C_5-C_6 cyclic group, C_1-C_4 alkyl and C_1-C_4 alkyl containing, and/or linked to the cyclic group through, an in-chain O, the aforesaid alkyl groups optionally being substituted by a substituent selected from halogen, amino, nitro, hydroxy and a C_5-C_6 cyclic group, and optionally said 5 to 13-membered cyclic group is aromatic or heteroaromatic, e.g. is phenyl or a 6-membered heteroaromatic group, for example X is benzyloxycarbonyl.

16. A dosage form of claim 10 or claim 15 wherein the boronic acid is of formula (VIII):

X-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$ (VIII).

17. A dosage form of any of claims 9 to 16 wherein the salt comprises a salt of the boronic acid with a metal.

18. A dosage form of claim 17 wherein the metal comprises an alkali metal salt, e.g. sodium, potassium or lithium.

19. A dosage form of any of claims 1 to 18 which comprises boronate ions derived from the peptide boronic acid and has a stoichiometry consistent with the boronate ions carrying a single negative charge.

20. A dosage form of any of claims 1 to 19 which comprises:

a pharmaceutical formulation which contains said compound and is in the form of powder or granules; and

a sealed container in which the formulation is contained and from which the formulation is to be dispensed for reconstitution.

21. A dosage form of claim 20 wherein the formulation is in the form of a powder and comprises a flow aid or a glidant.

22. A dosage form of claim 20 wherein the formulation is in the form of granules and comprises a binder.

23. A dosage form of any of claims 20 to 22 wherein the container is a sachet.

24. A dosage form of any of claims 1 to 19 which comprises a pharmaceutical formulation which is in the form of an effervescent tablet which contains said compound and an effervescent system.

25. A dosage form of any of claims 1 to 19 which comprises a fast melt pharmaceutical formulation which contains said compound.

26. A dosage form of any of claims 20 to 25 which comprises from about 0.2 to about 1.5 mol of the compound, calculated on the basis of the boronic acid, e.g. about 0.35 to about 1 mol.

27. A dosage form of any of claims 1 to 26 which comprises an anti-microbial preservative and a flavour agent.

28. A dosage form of any of claims 1 to 23, or claims 26 or 27 when not dependent on claim 26, which is adapted to be reconstituted to form a solution having a volume of from about 50ml to about 150ml.

29. A pharmaceutical formulation comprising a pharmaceutically acceptable base addition salt of the acid Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$, the formulation being in the form of a powder or granules in a sachet or of an effervescent tablet.

30. A method of making an oral dosage form for preventing thrombosis, comprising:

reacting a boronic acid which has a neutral thrombin P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites with a base selected from the group consisting of basic metal compounds, e.g. a metal hydroxide or carbonate, and organic nitrogen-containing compounds having a pKb of at least 7, to form a reaction product; and

formulating the reaction product into a solid phase formulation which comprises the reaction product and is adapted for reconstitution of the formulation to form a liquid preparation.

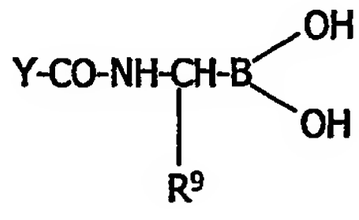
31. The use of a compound as defined in any of claims 1 to 19 for the manufacture of a medicament to be reconstituted to form a drinkable preparation, e.g. a drinking solution.

32. The use of claim 31 wherein the medicament is for use in the prevention of thrombosis in the haemodialysis circuit of a patient undergoing haemodialysis.

33. The use of claim 31 wherein the medicament is for emergency treatment of a suspected thrombotic event.

34. A method of preparing an anticoagulant preparation, comprising reconstituting, into a liquid preparation for oral administration and preferably a drinkable preparation, a solid phase formulation comprising:

a) a first species selected from (a) boronic acids of formula (I) below, (b) boronate anions thereof, and (c) any equilibrium form of the aforegoing (e.g. an anhydride), and combinations thereof:



(I)

wherein

Y comprises a hydrophobic moiety which, together with the aminoboronic acid residue $-NHCH(R^9)-B(OH)_2$, has affinity for the substrate binding site of thrombin; and

R^9 is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or R^9 is $-(CH_2)_m-W$ where m is from 2, 3, 4 or 5 and W is –OH or halogen (F, Cl, Br or I); and

(b) a second species selected from the group consisting of pharmaceutically acceptable metal ions, said metal ions having a valency of n, and strongly basic organic nitrogen-containing compounds.

35. A method of inhibiting thrombin in the treatment of disease, comprising administering perorally to a subject in need thereof a therapeutically effective amount of a compound as defined in any of claims 1 to 19, said compound being put into solution or suspension from a solid phase formulation prior to the compound entering the stomach.

36. The method of claim 35, wherein the salt is put into solution or suspension by reconstituting with a liquid prior to administration or in saliva in the mouth.

37. A method of preventing thrombosis in the haemodialysis circuit of a patient, comprising reconstituting into a drinkable preparation a solid formulation comprising a salt as defined in any of claims 9 to 19, and orally administering the drinkable preparation.

38. The use of a compound as defined in any of claims 1 to 19 for the manufacture of a medicament for treating flight DVT or thrombosis in intermittent apheresis, e.g. extracorporeal liver detoxification.

39. The use of claim 38, wherein the medicament is an oral medicament, for example a tablet, capsule, sachet, effervescent tablet or fast melt formulation, or is a parenteral medicament, e.g. an i.v. medicament, for example a powder.

40. A method of preventing deep vein thrombosis during an airplane flight in a subject at risk of developing such thrombosis, comprising administering to the subject a therapeutically effective amount of a compound as defined in any of claims 1 to 19.

41. A method of preventing thrombosis in extracorporeal liver detoxification in a subject at risk of developing such thrombosis, comprising administering to the subject a therapeutically effective amount of a compound as defined in any of claims 1 to 19.

42. The use, for the manufacture of a medicament for the prevention of thrombosis in the haemodialysis circuit of a patient undergoing haemodialysis, of a compound selected from boronic acids which have a neutral thrombin P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, and salts, prodrugs and prodrug salts of such acids, the compound not being a base addition salt of such a boronic acid.